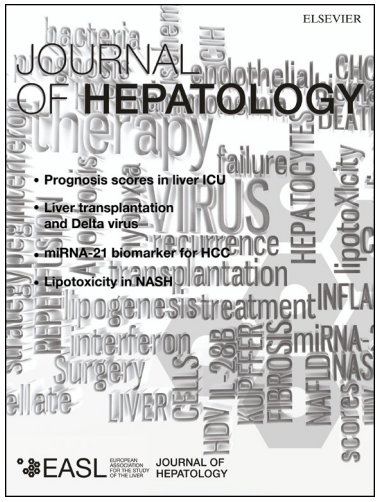

Letter to the Editor

Reply to: "From the CUPIC study: Great times are not coming (?)"

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PII: S0168-8278(13)00889-1
DOI: http://dx.doi.org/10.1016/j.jhep.2013.12.020
Reference: JHEPAT 4983

To appear in: *Journal of Hepatology*

Received Date: 16 December 2013
Revised Date: 18 December 2013
Accepted Date: 19 December 2013

Please cite this article as: Hezode, C., Fontaine, H., Barthe, Y., Carrat, F., Bronowicki, J-P., Reply to: "From the CUPIC study: Great times are not coming (?)", *Journal of Hepatology* (2013), doi: http://dx.doi.org/10.1016/j.jhep.2013.12.020

Reply to: "From the CUPIC study: Great times are not coming (?)"

To the Editor:

Schmidt-Martin D and colleagues raised one comment regarding the main recommendation of our article meaning that patients with hypoalbuminemia (<35 g/dl) and thrombocytopaenia (≤100,000/mm^3) should not be treated with an interferon based triple therapy due to the high risk to develop severe complications during the first 16 weeks of therapy [1]. As mentioned in the supplementary materials, severe complications were defined as any of death, grade 3 or 4 infection, hepatic decompensation. The cause of death, the description of severe infections and hepatic decompensation were detailed in the results section. A severe infection (grade 3 or 4) was defined by an infectious episode needing hospitalisation or life-threatening. Among the 6 patients who died during the first weeks of treatment, 3 had hypoalbuminemia (<35 g/dl) and thrombocytopenia (≤100,000/mm3) and the 3 others either hypoalbuminemia or thrombocytopenia.

CUPIC was a cohort in setting of the French early access program explaining that all patients received antiviral therapy and the lack of control group. In five recent studies (including a meta-analysis) evaluating the natural history of cirrhotic patients with characteristics comparable to those from the CUPIC cohort, the annual incidence of deaths and/or liver decompensation varied from 6.2 to 11% on treatment, challenging the indication for triple therapy in this subgroup of patients [2-6]. In the subgroup of patients who combined both predictors of severe complications (albumin <35 g/dl and platelet count ≤100,000/mm^3), their occurrence was 44.1% during the first 16 weeks. We cannot exclude that this rate could increase overtime in patients receiving 48 weeks of therapy. This result strongly suggests that the risk to develop severe complications is higher in patients with both predictors treated with triple therapy compared to untreated cirrhotic patients. We agree that the lack of a control group does not allow us to distinguish between severe events caused by treatment from those caused by the cirrhosis itself. However, based on comparisons with other studies in cirrhotic patients, the rate of observed severe events was much higher in this particular

group of patient with advanced cirrhosis, low platelet count and low albumin level. Moreover severe infection is a relatively rare event in non-treated compensated viral cirrhosis. Therefore, it's likely that the treatment contributed to these events. We agree that international treatment guidelines [7-8] recommend starting triple therapy in HCV genotype 1 patients with compensated cirrhosis. However, these guidelines were based on efficacy and safety data reported in cirrhotic patients included in phase III clinical trials. A crucial point is that low platelets count and hypoalbuminemia were exclusion criteria for these studies, meaning that no safety data was available in such patients at the time of international guidelines. Moreover, it is important to note that patients included in the international telaprevir early access program patients had severe fibrosis (n = 741, Metavir F3 or Ishak 3-4) or compensated cirrhosis (n = 840, Child-Pugh Grade A) and no history of decompensated liver disease. Additionally, patients must have a platelet count of at least 90,000/mm^3 and albumin >35 g/L [9]. This study does not allow providing safety data in patients with both predictors of severe complications. Schmidt-Martin D and colleagues suggest that the poor safety profile in such patients could be explained by the large number of centres involved in the CUPIC cohort with variation in the treatment and monitoring protocols. However, there was no impact of the experience of the centre, evaluated by the number of treated patients (<5 *vs*. ≥5 patients) on the occurrence of severe complications and grade 3/4 anaemia (Hb <8 g/dl) or blood transfusion.

In summary, we have clearly identified a subgroup of patients with a high risk of severe complications raising the question as to whether these patients, who are the most in need of therapy, should be treated with triple therapy including boceprevir or telaprevir. In practice, the risk of developing severe complications or death should be carefully balanced against the likelihood of a virological response and subsequent improvement of survival. These patients could benefit from prophylaxis (antibiotics) of treatment complications and should undergo careful monitoring while on therapy. Alternatively, most of them can wait for all-oral, IFN-free regimens.

Conflict of interest

Jean-Pierre Bronowicki: consultancy and speaker fees from MSD, Janssen Christophe Hézode: consultancy and speaker fees from MSD, Janssen Hélène Fontaine: speaker fees from MSD, Janssen.

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